CASE REPORT

Dual Candida albicans and Cryptococcus neoformans fungaemia in an AIDS presenter: a unique disease association in the highly active antiretroviral therapy (HAART) era

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A case report of a patient who discovered his HIV infection concurrently with an advanced immunodeficiency and a dual Candida albicans and Cryptococcus neoformans fungaemia is discussed with reference to the changing epidemiology and clinical features of HIV infection and AIDS in the highly active antiretroviral therapy (HAART) era. The tendency to develop multiple concomitant AIDS-defining illnesses at the time of first hospitalisation seems to be an increasing feature in patients who remain unaware of or neglect their HIV disease and who are still at risk of opportunistic infections even with the availability of HAART.

Introduction

Since 1996, the introduction of potent combination antiretroviral regimens (highly active antiretroviral therapy, HAART) has had a significant impact on the natural history of HIV infection in industrialised countries. HAART led to an early, sharp drop in the absolute frequency of opportunist diseases related to a severe degree of HIV-associated immunodeficiency (as expressed by a CD4+ lymphocyte count <50–100 cells/µl), such as visceral candidosis and cryptococcosis, which represent the most common opportunistic fungal infections in AIDS [1–3].

However, an appreciable number of patients remain unaware of their HIV status, refuse antiretroviral therapy or show a poor adherence to HAART, and so remain at high risk of developing severe opportunistic disorders as a result of their persistently low CD4+ cell count [4, 5]. As a consequence, multiple AIDS-defining disorders may be discovered concurrently only at the time of the first hospitalisation of a patient with an extremely severe immunodeficiency.

Thus, 5 of 10 patients notified with AIDS at our tertiary care centre in the first 4 months of 2002 had an unknown or a neglected HIV infection. This led to a diagnosis of full-blown disease at the time of their first admission, when three-to-seven concomitant AIDS-defining illnesses were identified (R. Manfredi, unpublished data). A similar situation encompassing key diagnostic and therapeutic implications occurs in the developing world, but underlying causes and supporting factors appear to be substantially different [6].

The aim of this report is to describe a particular case of concurrent haematogenous Candida-Cryptococcus visceral and disseminated co-infection in a patient with undiagnosed HIV infection.

Case report

A 59-year-old male who reported multiple heterosexual contacts at risk for acquiring HIV infection during the previous years, and who was unaware of his HIV infection, was referred to the Emergency Service and was first hospitalised at the Division of Internal Medicine of the University Hospital as a result of a severely compromised clinical situation. The latter included: an irregular hyperpyrexia of 2 months duration that was resistant to multiple broad-
spectrum empiric antibiotic therapies; pancytopenia; bilateral interstitial-alveolar \textit{Pneumocystis carinii} and \textit{Staphylococcus aureus} pneumonia (confirmed by microscopy and culture performed on both sputum and broncho-alveolar lavage); a respiratory infection with a multiresistant \textit{Mycobacterium kansasii} strain (the isolate was sensitive only to protonamide and cyclolserine); and a severe cachexia (wasting syndrome) arising from a long-term dysphagia due to an erosive \textit{Candida albicans} oesophagitis. This patient came to our attention when HIV infection was confirmed by immuno-enzymic and immunoblotting assays.

From a mycological point of view, this patient suffered from extensive pharyngeal and oesophageal candidosis (ascertained by endoscopy and confirmed by direct microscopy, culture and histopathological assays) and a dual, concurrent septicaemia with \textit{Candida albicans} and \textit{Cryptococcus neoformans}, confirmed by repeated growth and identification of both these yeasts from multiple consecutive blood cultures subcultured on Saboraud agar. Cerebrospinal fluid examination was negative for cryptococcosis by microscopy and culture, as was a polysaccharide antigen test, which excluded meningeal and central nervous system localisation (the patient had no neurological symptoms). Both \textit{C. albicans} and \textit{Cr. neoformans} isolates were susceptible to all tested antymycotic agents (polyenes, imidazoles-triazoles and fluocytosine), as measured in a microbroth assay according to current NCCLS standards [7]. At the time of admission to our division, the severe HIV-associated immunodeficiency was expressed by a CD4+-lymphocyte count of 44 cells/\mu l. Plasma HIV viral load was $>500\,000$ copies of HIV-RNA/ml (as assessed by an ultrasensitive branched-DNA technique). The patient did not undergo any invasive therapeutic or diagnostic procedure (including use of central lines), before detection of his multiple opportunistic infections.

As a result of the concomitant dual \textit{Candida-Cryptococcus} visceral infection, treatment was instituted with high-dose fluconazole (800 mg/day for 10 days, followed by 400 mg/day), concurrent liposomal amphoterin B (3 mg/kg for the first 10 days) and topical nystatin for 8 weeks. This led to the disappearance of clinical signs and symptoms and mycological tests also became negative.

At the time of discharge – which occurred 8 weeks after admission because of a persisting fever, fatigue, sweating and weight loss attributable to the multi-resistant \textit{M. kansasii} disease – the CD4+ count had risen to 164 cells/\mu l and HIV viremia had dropped to 2000 copies/ml, because of the early introduction of a HAART regimen including stavudine, lamivudine and indinavir. After 4 months of follow-up, clinical and mycological examinations for \textit{Candida} and \textit{Cryptococcus} infection remained negative.

**Discussion**

Multiple, concomitant or subsequent AIDS-defining diseases have been anecdotally described to date as single case reports or very small series, usually focusing on in-vivo diagnostic difficulties [6, 8–10]. Most concurrent disorders may be undiagnosed after the first AIDS-defining diagnosis is made, especially when signs and symptoms of more than one opportunistic disease may overlap [3, 8, 11–13]. A recent study focusing on HIV-associated fungaemia reported only one case of associated \textit{C. albicans-C. glabrata} co-infection in blood cultures examined in a 12-year period at a large reference centre [14].

As a consequence, the concurrent detection of two different visceral yeast diseases associated with haematogenous dissemination (i.e., \textit{Candida-Cryptococcus} septicaemia) in the absence of cryptococcal meningo-encephalitis seems exceptional, as no previous reports are quoted in the international literature, with the exception of the above-mentioned mixed \textit{C. albicans-C. glabrata} haematogenous co-infection [14]. Moreover, the concomitant detection of further, important AIDS-defining disorders (i.e., pneumocystosis, atypical mycobacteriosis and wasting syndrome), makes this case report unique.

All five patients defined as ‘AIDS presenters’ at our division in 2002 who were suffering from multiple concurrent AIDS-defining disorders (including the above-mentioned patient) received HAART and an appropriate antimicrobial and supportive therapy, so that they benefited from a slow but progressive amelioration of HIV-related conditions. This was associated with an immunological recovery ranging from 60% to 500% in their CD4+ lymphocyte count, and a reduction of viremia ranging from 1.5 to 3.5 log_{10} HIV-RNA copies/ml compared with baseline, within 3 months of hospitalisation (R. Manfredi, unpublished data).

The present availability of very potent and varied antiretroviral therapeutic regimens has not impacted upon the persistent diagnosis of advanced cases of HIV disease, which continue to occur in patients who were unaware of their infection, in those who refused HAART or in those who had insufficient compliance with the prescribed antiretroviral therapy or antimicrobial prophylaxis [4, 5]. This alarming tendency seems related to epidemiological rather than clinical or therapeutical issues, but the introduction of HAART does not seem to have altered the proportional distribution of the majority of HIV-related opportunistic infections [4, 5]. Meanwhile the limited availability of HAART in the developing world means that AIDS patients are still at risk from opportunistic infections, including those of fungal origin [6].
References


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